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GB 2218336 A GB 1268658 A GB 1024648 A
EP 0035780 A1 EP 0008780 A2 US 4705695 A
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(54) Aqueous formulations for enteric coatings

(57) An aqueous formulation for enteric coating of pharmaceutical products comprises cellulose acetate phthelate, polyvinyl acetate phthalate, hydroxypropylmethyl cellulose phthalate, cellulose trimellitate or a methacrylic ecid-besed polymer, e salt-forming agent selected from 2-amino-2-methyl-1-propanol, N-methylflucamine, diethylemine, diethanolamine, N-benzylphenethylamine, 2-amino-2-methyl-1,3-propanediol, tertiary butylamine, 1-adamantanamine, N,N-dimethylethanolamine, 2-(ethylamino)ethanol, 3-methoxypropylamine and 1-[N,N-bis(2-hydroxyethyl)amino] -2-propanol, and a plasticiser selected from triethylcitrate, diethyl phthalate, triacetin and acetylated monoglycerida.

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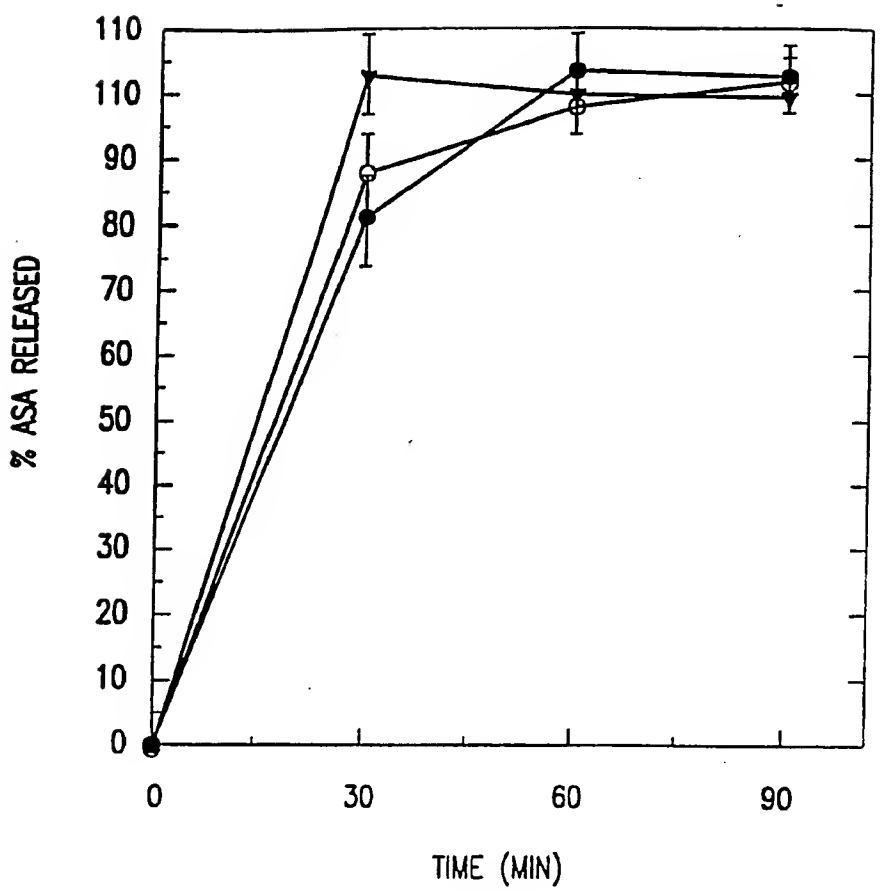

FIG.1

% ASA released as a function of time in pH 6.8 sodium phosphate buffer. Films were plasticized with 25% TEC. (●) 10%, (○) 8% and (▼) 6% weight gains. Mean ± S.D. (n=6). Film thicknesses were 165 μm, 135 μm and 91 μm for 10, 8 and 6% weight gains respectively.

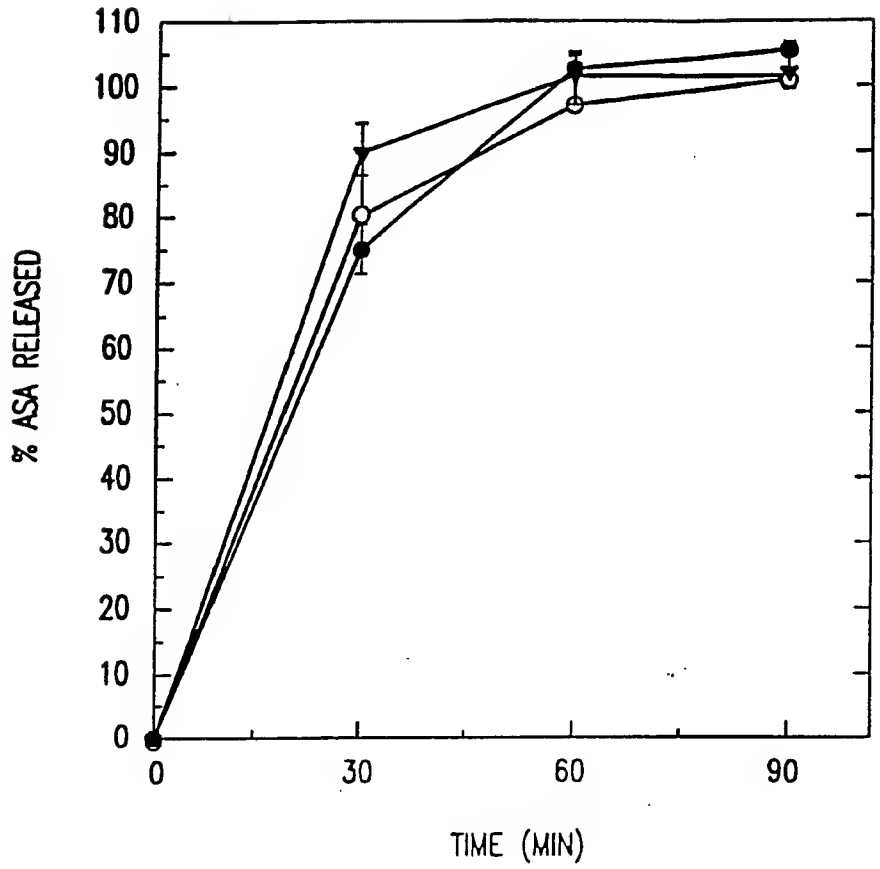

FIG.2

% ASA released as a function of time in pH 6.8 sodium phosphate buffer. Films were plasticized with 30% TEC. (●) 10%, (○) 8% and (▼) 6% weight gains. Mean ± S.D. (n=6). Film thicknesses were 175 μm, 130 μm and 90 μm for 10, 8 and 6% weight gains respectively.

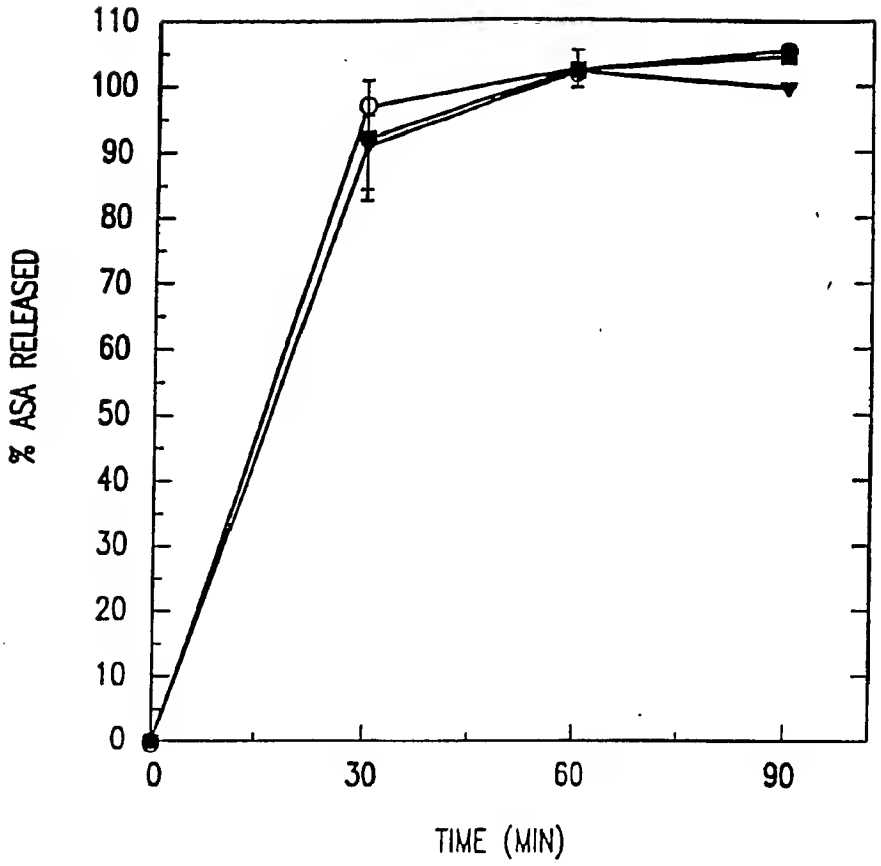

FIG.3

% ASA released as a function of time in pH 6.8 sodium phosphate buffer. Films were plasticized with 35% TEC. (●) 10%, (○) 8% and (▼) 6% weight gains. Mean ± S.D. (n=6). Film thicknesses were 143 μm, 123 μm and 78 μm for 10, 8 and 6% weight gains respectively.

TITLE OF INVENTION

AQUEOUS-BASED FORMULATIONS FOR ENTERIC COATED PRODUCTS

BACKGROUND OF THE INVENTION

Important functional properties of enteric film coatings are their water and drug permeabilites. Enteric coatings are primarily used to protect an acid-labile drug from stomach fluids or minimize drug induced gastric irritation. In the first case, the enteric film should obviously have low water permeability. On the other hand, when the intent is to minimize drug stomach exposure, a water permeable coating would still be satisfactory as long as a minimal amount of drug is released during the acid stage. In both cases, the film must be readily soluble in the second stage of testing i.e. alkaline buffer, so that the drug is readily available for systemic absorption.

Cellulose acetate phthalate (CAP), is a water insoluble polymer used for many years in organic solvent enteric coating formulations. With the gradual elimination of all organic solvents, such as acetone and methanol, in the pharmaceutical industry from the manufacturing of pharmaceutical drug products, there has been a growing need for aqueous-based coating technologies. Since CAP has low water solubility, its formulation into an aqueous system is challenging. See Eastman Kodak Co., Enteric Polymers. Publication No. EFC-202A, November 1991, stating CAP contains about 35% phthalyl and 24% acetyl groups. The polymer is insoluble in its non-ionized form, which predominates in acid, but becomes soluble as the phthalic acid groups become ionized above pH 6.

The methods proposed over the years to develop aqueous CAP coating solutions have focused primarily on the formation of soluble salts with sodium hydroxide (UK Pat. 2,057,876), triethanolamine (UK Patent 2,057,876) or ammonium hydroxide (Eastman Kodak, 1991; Chang, R-K., Pharm. Tech., Oct. (1990) 62-70; UK Pat. 2,057,876). See also Stafford, J., Drud Dev. & Ind. Pharm., 8:4 (1982) 513-530 where neutralized aqueous solutions of

hydroxypropyl methylcellulose phthalate are used. These solutions can be sprayed onto tablets after proper plasticization. Little attention has been given to these CAP solutions, probably because of the alternative latex systems available. However, CAP coating solutions have many advantages over latices: (1) they are not prone to shear-induced coagulation; (2) solutions are easier to transfer to a production environment than dispersions and (3) they are more cost-efficient.

The present invention relates to novel formulations of an aqueous-soluble salt of CAP which can be atomized onto tablets producing a film that is insoluble in acid but soluble in an alkaline buffer. The formulations can be used for any drug that requires an enteric film coating such as the manufacture of delayed release articles.

SUMMARY OF THE INVENTION

The present invention relates to a novel formulation of a pharmaceutically acceptable salt forming agent, water and a polymer for enteric coating of pharmaceutical products. The salt forming agent belongs to the group consisting of 2-amino-2 methyl-1-propanol (MAP), N-methylflucamine, diethylamine, diethanolamine, N-benzylphenethylamine, 2-amino-2-methyl-1,3-propandiol, tert-butylamine, 1-adamantanamine, N,N-dimethylethanolamine, 2-(ethylamino)ethanol,3 methoxypropylamine 1-[N,N-bis(2-hydroxyethyl)amino]-2-propanol, and the like, preferrably MAP, which unexpectedly neutralizes and dissolves the polymer in water. The polymers useful for this invention are cellulose acetate phthalate (CAP), polyvinyl acetate phthalate, hydroxypropylmethyl cellulose phthalate, cellulose acetate trimellitate, methacrylate methacrylic acid-based polymers, and the like, preferrably CAP. The formulation also contains a plasticizer belonging to the group consisting of triethylcitrate (TEC), diethylphthalate, triacetin, acetylated monoglycerides, and the like, preferrably TEC. The preferred formulation comprises MAP, CAP, water and from about 20% to about 35% TEC (based on CAP), preferrably from about 20% to about 30%, most preferrably 25%, which results in the release of $\leq$ 1% of a drug after about two hours in

0.1 N of an acid such as HCL and > 95% after from about 30 minutes to an hour in a buffer, thereby demonstrating excellent enteric coating properties for coating pharmaceutical products. Accordingly, it is an object of this invention to describe the composition of the instant novel formulation. An additional object is to describe the active components and additional components which may be employed in the formulation. Still another object of this invention is to provide a method using and testing the formulation. Additional objects of this invention will be apparent to persons of ordinary skill in the art upon reading the following detained description and appended claims.

DESCRIPTION OF THE DRAWINGS

Figures 1-3 show % ASA released, varying the %TEC, with respect to time in pH 6.8 sodium phosphate buffer.

DETAILED DESCRIPTION OF THE INVENTION

This invention consists of a novel formulation of a water-based salt forming agent such as 2-amino-2-methyl-1-propanol (MAP), N-methylflucamine, diethylamine, diethanolamine, N-benzylphenethylamine, 2-amino-2-methyl-1,3-propandiol, tert-butylamine, 1-adamantanamine, N,N-dimethylethanolamine, 2-(ethylamino)ethanol, 3methoxypropylamine, 1-[N,N-bis(2-hydroxyethyl)amino]-2-propanol, and the like, preferrably MAP, water, a polymer belonging to the group consisting of cellulose acetate phthalate (CAP), polyvinyl acetate phthalate, hydroxypropylmethyl cellulose phthalate, cellulose acetate trimellitate, methacrylate methacrylic acid-based polymers, and the like, preferrably CAP, and a plasticizer belonging to the group consisting of triethylcitrate (TEC), diethylphthalate, triacetin, acetylated monoglycerides, and the like, preferrably TEC, for enteric coating of pharmaceutical products. The polymers useful for this invention are those insoluble polymers containing a sufficient number of acid groups or having a high

dielectric constant. All percentages disclosed herein are expressed as % by weight.

MAP is found in a number of over- the -counter (OTC) products containing pamabrom (Barnhart, E.R., Physicians Desk Reference, Oradell, 43rd Ed., 1989, p.1005.) which is 2-amino-2-methylpropan-1-ol 8-bromotheophyllinate (Reynolds, J.E.F., Ed., Martindale, The Extra Pharmacopoeia, 29th ed., 1989, p.1598.), a mild diuretic that has been used for the relief of premenstrual tension. MAP (95%) can be obtained commercially, for example from Aldrich Chemical Company, Wisconsin. The instant formulation generally will contain from about 0.1 to about 50% of MAP (based on CAP) to dissolve the CAP, preferrably from about 15% to about 40%, most preferrably about 25% based on CAP, corresponding to from about 0 to 250% acid group molar excess, preferrably about 25% acid group molar excess.

Cellulose acetate phthalate (CAP), is a water insoluble polymer used for many years in organic solvent enteric coating formulations and is also commercially available (Eastman Chemical Co., TN). The polymer is insoluble in its non-ionized form, which predominates in acid, but becomes soluble as the phthalic acid groups become ionized above pH 6. The instant formulation generally will contain from about 1 to 20% of CAP in solution.

The plasticizers improve film characteristics and reduce defects in film coatings. Plasticizers lower the Tg of the polymer, which is defined as the onset of molecular mobility of the polymer segments, by increasing the molecular free volume. The plasticizer will preferrably have low vapour pressures, low diffusion rates within the polymer, will be pharmaceutically acceptable. The Formulation can contain from about 10% to about 50% of plasticizer, based on CAP, preferrably from about 10% to about 35%. The Tg for CAP alone is reported to be between 171°C (Sinko, C.M., Yee, A.F. and Amidon, G.L., Pharm. Res., 8:6 (1990) 698-705.), and 175°C (Eastman Kodak Co.).

The polymer/salt forming agent (SFA) formulation is prepared by dispersing the polymer in from about 1/2 to about 3/4 of the total amount of required water, preferrably about 2/3 of the required water. The amount of polymer added is calculated to make from about 1% to about 20% solution after addition of water to reach the final weight, preferrably about a 5% to 10% solution of polymer. SFA, from about 0.1% to about 50% of polymer is then poured into the dispersion and the mixture agitated for 0 to 4 hours to allow for complete dissolution of the polymer. The plasticizer is then added at 10-35% levels, based on polymer, preferrably about 20% to 30%, and water is added to reach the final weight. The solution is then agitated for about one minute to about one hour, preferrably about 30 minutes, to achieve plasticization of the polymer and then optionally passed through a 20-60-mesh screen, resulting in a plasticized polymer/SFA solution which is clear, free from any insoluble material and used within 48 hours following preparation, preferrably within 24 hours.

EXAMPLE OF THE INVENTION

A cellulose acetate phthalate (CAP)/2-amino-2-methyl-1-propanol (MAP) solution was formulated by dispersing CAP in approximately 2/3 of the total amount of required water, (the amount of CAP added was calculated to make an 8% solution after the final addition of water), adding 25% MAP, based on CAP, agitating the mixture for one hour, adding 20-35% triethylcitrate (TEC), based on CAP, to obtain plasiticized polymer solutions, adding water to reach the final weight, agitating the solution for 30 minutes and passing the solution through a 40-mesh screen to give a clear plasticized CAP/MAP solution. For comparison studies, ammoniated CAP solutions were prepared using the same method by adding a 30% ammonium hydroxide solution (American Chemical Ltd. Quebec) at a 19% level based on CAP.

The following are nonlimiting examples of the MAP/CAP composition of the present invention. The indicated percentages of MAP and TEC are based on CAP.

Composition I -

8%	CAP
25%	MAP
25%	TEC
q.s.	H_2O

Composition II -

10%	CAP
30%	MAP
20%	TEC
q.s.	H_2O

Evaluation of the Films

Plasticized and unplasticized polymer solutions were cast on poly(methyl methacrylate) film holders (62 cm^2) to make 0.15-0.2 mm films. The films were dried at ambient conditions for 14-16 hours. A final drying step was carried out in a convection tray dryer set at 45°C for 6-8 hours. The dry films were finally detached from the holders and stored in a desiccator under calcium sulphate. The physical stability of ammoniated CAP and CAP/MAP films was evaluated by monitoring the time required for dissolution in a 50 mM sodium phosphate buffer adjusted to pH 6.3-6.8. Films that were plasticized with 20%-35% TEC (based on CAP) were placed (app. 50 mg) in 20 ml glass vials and stored at 40 and 50°C stations over a 30-day period. At pre-determined time intervals, films were evaluated for dissolution in 10 ml of buffer under mild agitation (ca. 30 inversions per minute). See Table 1 below.

Table I shows the physical stability data for CAP/MAP and ammoniated CAP films. Ammoniated films showed a marked increase in dissolution time after 5 days of storage at 50°C. Insoluble, swollen clear films were obtained after 12 days at 50°C. Even when stored at 40°C for 30 days, insoluble material was still present one hour exposure to a 50 mM, pH 6.8 sodium phosphate buffer. Notable improvement in

the physical stability with respect to dissolution times was obtained using the MAP salt of CAP, when compared to ammoniated CAP. When stored at 40°C for up to 30 days, the dissolution time of the CAP/MAP films increased only slightly (15-20 minutes) while that for ammoniated CAP films increased significantly (60 minutes). Even with the films being stored at 50°C for 12 days the CAP/MAP films distintegrated in only 60-120 minutes with insoluble material present compared to 24 hours for ammoniated CAP films.

TABLE 1

PHYSICAL STABILITY OF CAP/MAP AND AMMONIATED CAP FILMS[1]

	CAP/MAP	AMMONIATED CAP
INITIAL	< 5 MIN.	< 5 MIN.
5 DAYS		
40°C	< 10 MIN.	10-15 MIN.
50°C	< 10 MIN.	45-60[2] MIN.
12 DAYS		
40°C	< 10 MIN.	< 10 MIN.
50°C	60-120[2] MIN.	> 24 HRS[3]
30 DAYS		
40°C	15-20 MIN.	1 HR[2]
50°C	> 24HRS[4]	> 24 HRS[5]

[1] time required to dissolve app. 50 mg of film in pH 6.8 sodium phosphate buffer

[2] disintegrated but insoluble material remaining in suspension

[3] brown discoloration, totally insoluble after 24hrs, clear film after exposure to buffer

[4] swollen clear film but insoluble after 24 hours

brown discoloration, totally insoluble after 24 hours, beige opaque film ater exposure to buffer

Assessing the Enteric Integrity of the CAP/MAP films

Acetylsalicyclic acid (ASA) tablets were used as a classical drug model to assess the enteric integrity of sprayed CAP/MAP films. ASA tablets (650 mg) were compressed with 16x9 mm (0.623 x 0.341-inch) oval plain punches. Tablet physical parameters such as weight, hardness (Model HT300, Key, NJ) and thickness were measured. Tablet thickness was determined with a precision of ± 0.001 mm using a digital micrometer (Mitutoyo, NJ). The tablets were coated (12-inch pan, Labcoat II system, O'Hara Manufacturing, Ontario) at 6, 8 and 10% theoretical film weight gains using process parameters shown in Table II below. Three levels of plasticizer (25, 30 and 35%) were evaluated for each film weight gain. Film thickness (n=20) was determined by the same method as for the core tablets. Physical evaluation of films sprayed onto ASA tablets was performed by scanning electron microscopy (model JSM-820, Jeol USA Inc., MA).

The core tablet weight, hardness and thickness were found to be 777±8 mg (mean±S.D.), 19.1± 0.5 Kp and 6.85± 0.04 mm, respectively. The tablet surface area as determined from punch drawings and tablet thickness was 3.07 cm^2. Films that were sprayed onto ASA tablets were homogeneous, dense and free from cracks and pores. Film thickness ranged from 78-91 µm, 123-135 µm and 143-175 µm for tablets that were coated with 6, 8 and 10% weight gains, respectively.

TABLE II

FILM COATING PROCESS PARAMETERS

Batch Size:	1 kg
Nozzle[1]:	air: 67228-45; liquid: 2850
Inlet Temperature:	60°C
Air Volume:	250 scfm
Inlet Air Dew Point:	9-15°C
Spray Rate:	8-10 g/min
Atomizing Pressure:	1 bar
Pan Differential Press:	-0.1 kPa
Pan Speed:	16 rpm
Outlet Temperarture:	40-45°C
Drying:	10 minutes at 2 rpm, heat on

[1] Flat spray, Spraying Systems Co., Quebec

Film Coating Functional Testing

Core tablets released 95.4% ± 5.2 (S.D., n=6) ASA after 30 minutes in acid, showing that the drug was readily available from the formulation. Regardless of film thickness and TEC level, all coated tablets released ≤ 1% of ASA after two hours exposure to acid, thereby demonstrating the excellent enteric integrity of the CAP/MAP films using conventional pan coating technology. Figures 1-3 show % ASA released with respect to time in pH 6.8 sodium phosphate buffer. Virtually 100% of ASA was released after 60 minutes, indicating solubilization of the film. For films that were plasticized with 25 and 30% TEC(based on CAP), there was a trend between the thickness and the amount of ASA released after 30 minutes. Tablets coated with films that were sprayed at a 6% weight gain level released the drug faster than films sprayed at 10% level. The results also demonstrates that with all dosage forms less than 10% drug release in acid after 2 hours and more than 80% drug release in buffer after 90 minutes was obtained.

Examples of beneficial drugs that may be adapted for use in the instant formulation are disclosed in Remington's Pharmaceutical Sciences, 16th Ed., 1980, published by the MacMillan Company, London; and in The Merck Index, 11th Edition, 1989, published by Merck & Co., Rahway, N.J. The dissolved drug can be in various forms, such as charged molecules, charged molecular complexes or ionizable salts. Acceptable salts include, but are not limited to hydrochlorides, hydrobromide, sulfate, laurylate, palmitate, phosphate, nitrate, borate, acetate, maleate, malate, succinate, tromethamine, tartrate, oleate, salicylate, salts of metals, and amines or organic cations, for example quaternary ammonium.

Derivatives of drugs such as esters, ethers and amides without regard to their ionization and solubility characteristics can be used alone or mixed with other drugs. Also, a drug can be used in a form that upon release from the device, is converted by enzymes, hydrolyzed by body pH or other metabolic processes to the original form, or to a biologically active form.

Specific examples of drugs that may be adapted for use include, Angiotensin-converting enzyme (ACE) inhibitors such as enalapril, lisinapril, and captopril; barbiturates such as pentobarbital sodium, phenobarbital, secobarbital, thiopental and mixtures thereof; heterocyclic hypnotics such as dioxopiperidines and glutarimides; hypnotics and sedatives such as amides and ureas, exemplified by diethylisovaleramide and α-bromoisovaleryl urea; hypnotic and sedative urethanes and disulfanes; psychic energizers such as isocarboxazid, nialamide, imipramine, amitryptyline hydrochloride, pargylene, and protryptyline hydrochloride; tranquilizers such as chloropromazine, promazine, fluphenzaine, reserpine, deserpidine, and meprobamate; benzodiazepines such as diaepam and chlorodiazepoxide; anticonvulsants such as primidone, phenytoin, and ethosuximide; muscle relaxants and antiparkinson agents such as mephensin, methocarbomal, cyclobenzaprine hydrochloride, trihexylphenidyl hydrochloride, levodopa/carbidopa, and biperiden; antihypertensives such as α-methyldopa and the pivaloyloxyethyl ester of α-methyldopa; calcium

channel blockers such as nifedipine, felodipine, diltiazem hydrochloride, diltiazem malate and verapamil hydrochloride; analgesics such as morphine sulfate, codeine sulfate, meperidine, and nalorphine; antipyretics and antiinflammatory agents such as aspirin, indomethacin, ibuprofen, sodium indomethacin trihydrate, salicylamide, naproxen, colchicine, fenoprofen, sulindac, diflunisal, diclofenac, indoprofen and sodium salicylamide; local anesthetics such as procaine, lidocaine, tetracaine and dibucaine; antispasmodics and muscle contractants such as atropine, scopolamine, methscopolamine, oxyphenonium, papaverine; prostaglandins such as PGE_1, PGE_2, PGF_{2a}; antimicrobials and antiparasitic agents such as penicillin, tetracycline, oxytetracycline, chlorotetracycline, chloroamphenicol, thiabendazole, ivermectin, and sulfonamides; antimalarials such as 4-aminoquinolines, 8-amino-quinolines and pyrimethamine; hormonal and steroidal agents such as dexamethasone, prednisolone, cortisone, cortisol and triamcinolone; androgenic steroids such as methyltestosterone; estrogenic steroids such as 17α-estradiol, α-estradiol, estriol, α-estradiol 3-benzoate, and 17-ethynyl estradiol-3-methyl ether; progestational steroids such as progesterone; sympathomimetic drugs such as epinephrine, phenylpropanolamine hydrochloride, amphetamine, epherdrine and norepinephrine; hypotensive drugs such as hydralazine; cardiovascular drugs such as procainamide hydrochloride, amyl nitrite, nitroglycerin, dipyridamole, sodium nitrate and mannitol nitrate; diuretics such as chlorothiazide, acetazolamide, methazolamide, hydrochlorothiazide, amiloride hydrochloride and flumethazide, sodium ethacrynate, and furosemide; antiparasitics such as bephenium, hydroxynaphthoate, dichlorophen and dapsone; antineoplastics such as mechlorethamine, uracil mustard, 5-fluorouracil, 6-thioguanine and procarbazine; β-blockers such as pindolol, propranolol, metoprolol, oxprenolol, timolol maleate, atenolol; hypoglycemic drugs such as insulin, isophane insulin, protamine zinc insulin suspension, globin zinc insulin, extended insulin zinc suspension, tolbutamide, acetohexamide, tolazamide and chloropropamide; antiulcer drugs such as cimetidine, ranididine, famotidine and omeprazole; nutritional agents such as ascorbic acid,

niacin, nicotinamide, folic acid, choline, biotin, panthothenic acid; essential amino acids; essential fats; ophthalmic drugs such as timolol maleate, pilocarpine nitrate, pilocarpine hydrochloride, atropine sulfate, scopolamine; electrolytes such as calcium gluconate, calcium lactate, potassium chloride, potassium sulfate, sodium fluoride, ferrous lactate, ferrous gluconate, ferrous sulfate, ferrous fumerate and sodium lactate; and drugs that act on α-adrenergic receptors such as clonidine hydrochloride; analgesic drugs such as acetaminophen, oxycodone, hydrocodone, and propoxyphene; antihypercholesterolemic drugs such as simvastatin, pravastatin, lovastatin and gemfibrozil; antiinfective drugs uch as cefoxitin, cefazolin, cefotaxime, ciprofloxacin, cephalexin, norfloxacin, amprolium, ampicillin, amoxicillin, cefaclor, erythromycin, nitrofurantoin, minocycline, doxycycline, cefadroxil, miconazole, clotrimiazole, phenazopyridine, clorsulon, fludalanine, pentizidone, cilastin, phosphonomycin, imipenem; gastrointestinal drugs such as bethanechol, clindinium, dicyclomine, meclizine, prochloroperizine, trimethobenzamide, loperamide, diphenoxylate, and metoclopramide; anticoagulant drugs such as warfarin, phenindione, and anisidione; 5 α-reductase inhibitors such as PROSCAR® and other drugs such as trientine, cambendazole, ronidazole, rafoxinide, dactinomycin, asparaginase, nalorphine, rifamycin, carbamezapine, metaraminol bitartrate, allopurinol, probenecid, diethylpropion, dihydrogenated ergot alkaloids, nystatin, pentazocine, phenylpropanolamine, phenylephrine, pseudoephedrine, trimethoprim, and ivermectin.

The above list of drugs is not meant to be exhaustive. Many other drugs and drug combinations will certainly work in the instant invention.

By "therapeutically effective amount" is meant that the quantity of beneficial agent, contained in the core, which can be delivered to the environment of use, has been demonstrated to be sufficient to induce the desired effect during studies utilizing the beneficial agent.

Other excipients such as lactose, magnesium stearate, microcrystalline cellulose, starch, steariid, calcium phosphate, blycerol monosterate, sucrose, polyvinylpyrrolidone, gelatin, methylcellulose, sodium carboxymethylcellulose, sorbitol, mannitol, polyethylene glycol and other ingredients commonly utilized as stabilizing agents or to aid in the production of tablets may also be present in the core.

The drug can be in the core as a dispersion, particle, granule, or powder.

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WHAT IS CLAIMED IS:

1. A formulation comprising from about 1 to about 20% solution of a polymer comprising cellulose acetate phthalate (CAP), polyvinyl acetate phthalate, hydroxypropylmethyl cellulose phthalate, cellulose acetate trimellitate, methacrylate methacrylic acid-based polymers, from about 0.1 to about 50%, by weight based on the polymer, of a salt forming agent comprising 2-amino-2 methyl-1-propanol (MAP), N-methylflucamine, diethylamine, diethanolamine, N-benzylphenethylamine, 2-amino-2-methyl-1,3-propandiol, trt-butylamine, 1-adamantanamine, N,N-dimethylethanolamine, 2-(ethylamino)ethanol, 3-methoxypropylamine, 1-[N,N-bis(2-hydroxyethyl)amino]-2-propanol, based on the polymer and corresponding to from about 0 to about 250% acid group molar excess, from about 10 to about 50% of a plasticizer comprising triethylcitrate (TEC), diethylphthalate, triacetin, acetylated monoglycerides, based on the polymer and a volume of water required to make from about 1% to about 20% of polymer solution for enteric coating of pharmaceutical products.

2. The formulation according to Claim 1 wherein the polymer is cellulose acetate phthalate and the salt forming agent is 2-amino-2-methyl-1-propanol.

3. The formulation according to Claim 1 which contains from about 20 to about 30% 2-amino-2-methyl-1-propanol based on cellulose acetate phthalate, corresponding to from about 15 to 35% acid group acid molar excess.

4. The formulation according to Claim 1 wherein the plasticizer is from about 10 to about 35% of triethylcitrate.

5. A waterbased cellulose acetate phthalate formulation consisting of from about 1 to about 20% of cellulose acetate phthalate,

from about 0.1 to about 50% of 2-amino-2-methyl-1-propanol based on the cellulose acetate phthalate and corresponding to from about 0 to about 250% acid group molar excess, from about 10, to about 50% of triethylcitrate, based on cellulose acetate phthalate, and a volume of water required to make from about 1% to about 20% of polymer solution for enteric coating of pharmaceutical products.

6. The process for the preparation of the formulation of Claim 1 which comprises dispersing the polymer in from about 1/2 to about 3/4 of the total amount of required water, the amount of polymer added calculated to make a 1 to 20% solution after final addition of water, adding from about 0.1 to about 50% of salt forming agent based on the polymer and corresponding to from about 0 to about 250% acid group molar access, agitating the mixture for 0 to 4 hours, adding from about 10 to 50% of the plasticizer based on the polymer, and adding the final volume of water.

7. The process of Claim 6 wherein the polymer is cellulose acetate phthalate, the plasticizer is triethylcitrate and the salt forming agent is 2-amino-2-methyl-1-propanol.

8. A process for the preparation of a water-based cellulose acetate phthalate which comprises dispersing cellulose acetate phthalate in from about 1/2 to about 3/4 of the total amount of required water, the amount of cellulose acetate phthalate added calculated to make a 1 to 20% solution after the final addition of water, adding from about 0.1 to about 50% of 2-amino-2-methyl-1-propanol, based on the cellulose acetate phthalate and corresponding to from about 0 to about 200% acid group molar access, agitating the mixture for 0 to 4 hours adding from about 10% to about 50% of triethylcitrate, based on cellulose acetate phthalate, and adding the final volume of water.

9. A method for enteric coating of pharmaceutical products which comprises applying the formulation of Claim 1 to the pharmaceutical product and drying the product.

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Patents Act 1977
Examiner's report to the Comptroller under Section 17
(The Search report) 18

Application number
GB 9501308.2

Relevant Technical Fields

(i) UK Cl (Ed.N) C3V (VAT, VAN, VET); A5B (BG)

(ii) Int Cl (Ed.6) A61K

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26 APRIL 1995

Databases (see below)
(i) UK Patent Office collections of GB, EP, WO and US patent specifications.

(ii) ONLINE: WPI

Documents considered relevant following a search in respect of Claims :-
1-9

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages		Relevant to claim(s)
Y	GB 2218336 A	(GLAXO) Claims 1 & 2	at least Claim 1
Y	GB 1268658	(SHINETSU) page 3, lines 32-62	at least Claim 1
Y	GB 1024648	(ELI LILLY) Claim 1	at least Claim 1
Y	EP 0035780 A1	(SHIN-ETSU) Claim 1	at least Claim 1
Y	EP 0008780 A2	(SHIN-ETSU) Claims 1, 9	at least Claim 1
Y	US 4705695	(RÖHM) Claim 1; column 2, lines 51-61	at least Claim 1
Y	US 4088798	(SANDOZ) Claim 1; column 5, lines 3-16	at least Claim 1

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).

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